Research

Multiparametric Imaging of Tumors – an Emerging Paradigm

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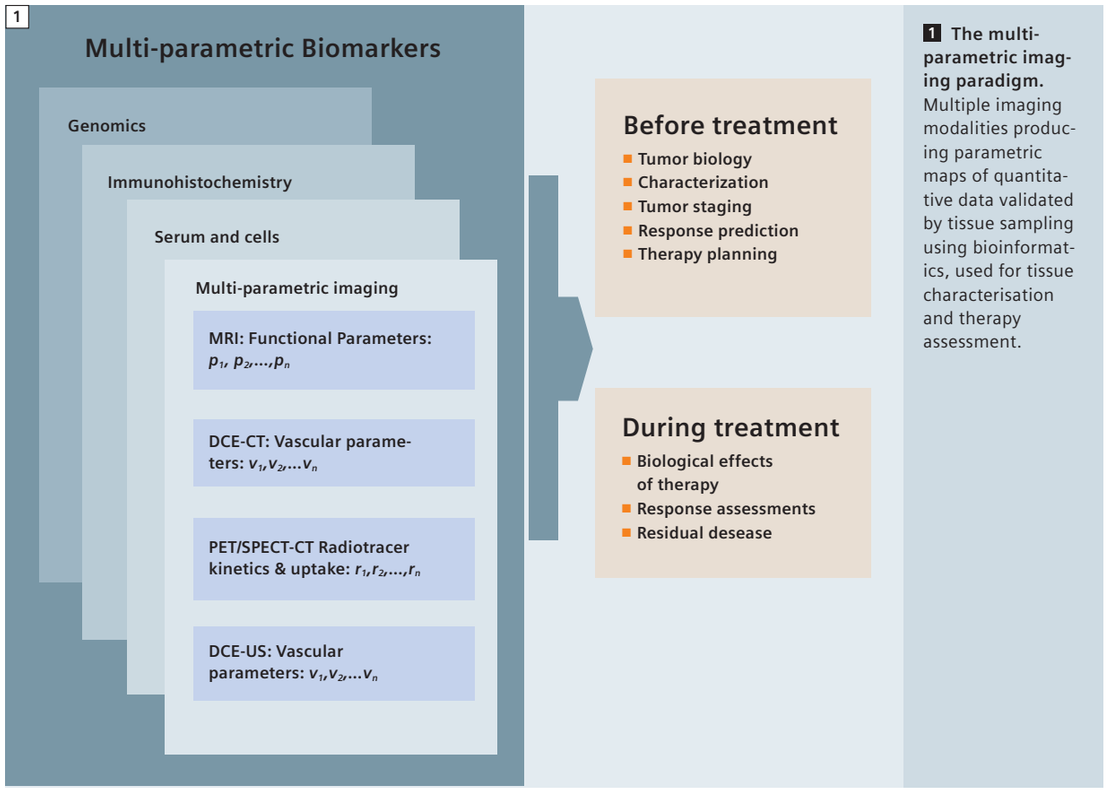
Introduction

To date, the main focus for innovations in imaging has been the achievement of excellence in anatomical resolution. In the field of cancer therapy response, morphological imaging is recognized to have significant limitations including the presence of tumors that cannot be measured, poor measurement reproducibility and mass lesions of unknown activity that persist following therapy. In neuro-oncology for example, the full extent of gliomas is poor depicted on contrast enhanced T1-images and by T2-FLAIR hyperintensity.
Anatomic imaging techniques may be insensitive to changes that inform on overall therapeutic success of cytostatic therapies, because the basic assumption that changes in tumor size reflect biological activity is violated. An example is pseudoresponse of glioblastomas treated with antiangiogenic therapy, where decreasing enhancement due to vascular normalization can be seen but with increasing mass effect and/or increasing tumor infiltration. The disconnection between anatomically determined progression free survival (PFS) and therapeutic efficacy (overall survival – OS) is recognized for a number of cytostatic therapies. The latter has recently resulted in a recommendation to withdraw the license to use the antiangiogenic drug bevacizumab for metastatic breast cancer by a committee of the US Food and Drug Administration (FDA), because improved PFS which was used for initial licensing did not ultimately result in improved OS. More sophisticated measurement methods such as tumor volume and CT density changes maybe unable to completely address these limitations.
Functional-molecular imaging methods made possible by the availability of MRI and PET scanners in particular have enabled many current clinical limitations to be addressed, as well as extending the applications of imaging in medicine. Thus, over the last decade we have seen the increasing use of functional-molecular imaging in the staging of patients with cancer and for monitoring their therapeutic response. Some of these functional-molecular imaging techniques are able to predict the success of therapy before conventional measurements of size are changed. Functional-molecular parameters are also being used as pharmacodynamic biomarkers in early phases of drug development (preclinical and clinical), in order to provide confidence to proceed to more expensive clinically studies of therapeutics with novel mechanisms of action. Advantages of functional-molecular imaging techniques include the fact that quantitative biomarkers obtained are spatially resolved, although resolution is in general less than corresponding anatomical images. Moreover functional-molecular imaging techniques are now beginning to identify the emergence of therapy resistance to a variety of treatments including novels drugs. An example of the latter is new internal enhancement on CT/MRI scans or ^{18}FDG-PET uptake in a size stable gastrointestinal tumor (GIST) treated with imatinib mesylate.
Examples of clinically deployed functional imaging MRI and PET techniques and the biological properties that they depict are given in tables 1 & 2. Reviews of the physical basis for MRI and PET and their differing sensitivity to depict biological processes, reveals that MRI is more suited to evaluating the structure and dynamic aspects of microenvironment of tissues (e.g., blood flow, vascular permeability, cell packing, necrosis and pH), some of which requires the administration of exogenous contrast agents or other methods of enhancing MRI sensitivity (e.g., by hyperpolarisation). On the other hand, because PET has a great sensitivity to compounds present at nanomolar or even picomolar concentrations but has a slower mode of acquisition, it more suited to evaluating cellular and molecular processes (depending largely on the radiotracers used). Until recently, these techniques were used mostly in isolation. However, there is now an increasing possibility to undertake multifunctional/multiplex imaging



1 The multi-parametric imaging paradigm. Multiple imaging modalities producing parametric maps of quantitative data validated by tissue sampling using bioinformatics, used for tissue characterisation and therapy assessment.

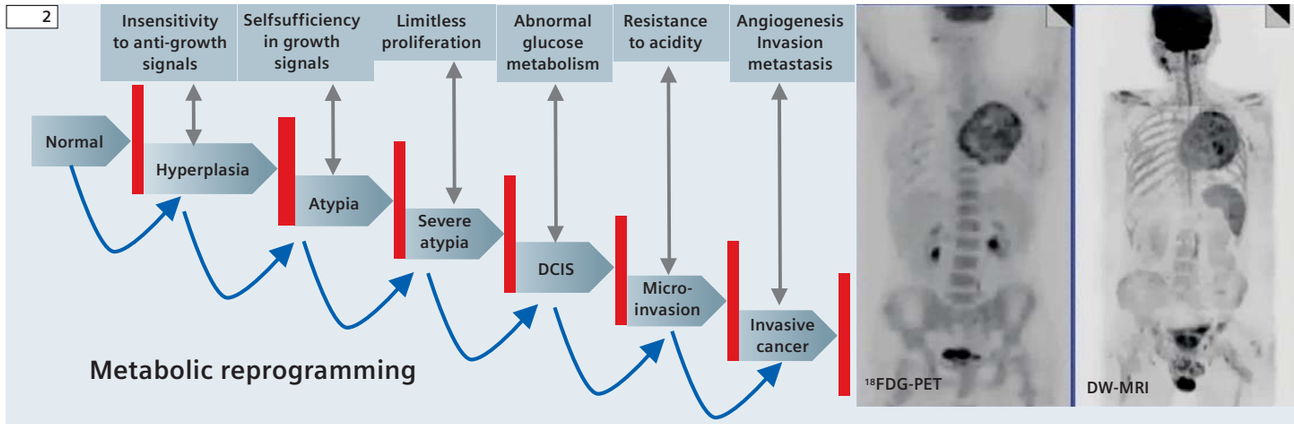
(Kobayashi, Longmire et al. 2010) for biological investigations in animals but also clinically (Antoch and Bockisch 2009; Padhani and Miles 2010).
Combined/multiplex approaches have been made possible by (a) the development of hybrid imaging technologies such as SPECT-CT and PET-CT and the soon to be available PET-MRI, (b) technological advancements within individual imaging modalities which enable multi-functional data acquisitions within short periods of time including the use of multiple PET isotopes with very short half lives, (c) advances in software enabling both fusion of imaging data between different imaging modalities and derivation of quantitative biologically relevant biomarker data that can be co-registered with anatomical images, and lastly (d) bioinformatics allowing integration of quantitative imaging parameters with other biological data such as serum cytokines, circulating cells and tissue genomic and protein expressions levels from targeted tissue biopsies (Figure 1).
We have come to recognize that the multiparametric imaging approach is fast becoming an important means for biological investigation because of its multi-dimensional (multispectral, multispatial and temporally resolved) nature. In this article we do not discuss the technological advances that have made multiparametric imaging a reality. Instead we will appraise the current clinical roles of multiparametric imaging for characterizing tumors and in the therapy response setting indicating the added value imparted by this new approach. In so doing we can gain insights into the potential future areas where multiparametric approaches with combined PET-MRI maybe able to take us both scientifically and clinically.

Imaging depiction of altered tumor biology

Observations show us that cancers are complex, evolving, multiscale systems that are characterized by profound spatial and temporal heterogeneity in their biological characteristics. Most clinically manifested invasive epithelial cancers have typical, hallmark characteristics as a result of genetic changes and metabolic reprogramming that enables pre-cancer lesions to develop into virulent invasive tumors, by successfully

Table 1: Summary of commonly available functional MRI techniques, the quantitative parameters derived and their biological correlates.

Functional Imaging Technique	Biological property on which imaging is based	Commonly derived quantitative imaging parameters/ biomarkers	Pathophysiological correlates
Diffusion-weighted MRI (DW-MRI)	Diffusivity of water	■ Apparent diffusion coefficient (ADC) ■ Fractional anisotropy (FA) ■ Water diffusivity (D) ■ Perfusion fraction (F_p)	Cell density and distribution of cell sizes, extracellular space tortuosity, gland formation, cell membrane integrity, necrosis, fluid viscosity
Dynamic contrast-enhanced MRI (DCE-MRI)	Contrast medium uptake rate in tissues, which is influenced by: ■ Perfusion & transfer rates ■ Extra-cellular volume ■ Plasma volume fraction	■ Initial area under gadolinium curve (IAUGC) ■ Transfer and rate constants (K^{trans}, k_{ep}) ■ Leakage space fraction (v_e) ■ Fractional plasma volume (v_p)	Vessel density Vascular permeability Perfusion Tissue cell fraction Plasma volume
Dynamic susceptibility contrast MRI (DSC-MRI)	Blood volume and blood flow	■ relative blood volume/ flow (rBV/rBF) ■ Mean transit times (MTT) ■ Vessel size index	Vessel density Blood flow Tumor grade Vessel diameter
^{1}H-MR spectroscopic imaging (^{1}H-MRSI)	Cell membrane turnover/energetics and replacement of normal tissues	■ Quantified ratios of metabolites including choline, creatine, lipids, citrate, lactate and others depending on echo time and tissues evaluated	Tumor grade Proliferation index
Blood oxygenation level dependent (BOLD) or intrinsic susceptibility-weighted (ISW) MRI	Deoxyhaemoglobin shows higher relaxivity than oxyhaemoglobin. Measurement also reflect blood volume, perfusion and Intrinsic composition of tissues	■ Intrinsic tissue relaxation rate (R2* =1/T2*)	Tissue susceptibility properties including air and bone interfaces, ferromagnetic properties and blood oxygenation



2 Carcinogenesis: hallmarks and metabolic reprogramming. In the transition from normal cells to clinically manifested invasive cancers, typically phenotypic characteristics become manifested (the hallmarks of cancers) resulting from metabolic reprogramming. Functional imaging techniques can depict these metabolic processes and cancer hallmarks at the tumor level, in peritumoral regions and at the organ/whole organism levels. The whole-body images on the right side of the image are of a patient with non-small cell lung cancer imaged with ^{18}FDG-PET and DW-MRI.

adapting or circumventing the body's natural microenvironmental barriers to uncontrolled proliferation (Figure 2). These hallmarks must be present in order to sustain tumor growth and for tumors to spread (Hanahan and Weinberg 2000). These genetic changes and metabolic reprogramming often occurs in a stepwise fashion as epithelial lesions develop from normal → hyperplasia → dysplasia → carcinoma-in-situ → local invasive cancers → metastatic cancers as described by Gatenby and Gillies (Gatenby and Gillies 2008). Imaging techniques can depict some of these molecular and functional aberrations (directly or by inference) within precancerous (e.g., polyps) and cancerous lesions, in peritumoral regions and at the organ/whole organism levels. Many key cancer hallmarks can be mapped including altered metabolism (including that of glucose, amino acids and nucleosides), tumor cell hyperproliferation and apoptosis, hypoxia, angiogenesis and aberrant neovascularity, local infiltration and distant metastases. Since there is a stepwise development of the biological aberrations in cancers so functional-molecular imaging tests maybe able to inform on the stage of development of lesions. By combining the information derived from a number of techniques, it becomes possible to build up a unique, multi-faceted phenotypic view of tumor evolution thus allowing improved characterizations (Figure 1). As many cancer hallmarks are also key anticancer targets, the role of functional-molecular imaging can be extended into the areas of drug development and for monitoring of the clinical effectiveness of therapeutics. The rationale for the latter being that decisions regarding continuation or discontinuation of a targeted therapy could rely on specific methods that image pathways being targeted. Resistance to conventional and novel therapies is highly dependent on the tumor microenvironment and on host-tumor interactions, so the potential exists for functional-molecular imaging to inform on which patients or lesions are more or less likely to continue to respond or to develop therapy resistance. This is made possible because functional-molecular imaging depictions including the displayed heterogeneity do reflect underlying gene-protein expressions in a number of cancer types.

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Table 2: Examples of radionuclide imaging techniques used for assessing tumors:

Radiotracer	Biological property on which imaging is based	Commonly derived quantitative imaging parameters/ biomarkers	Comments
^{18}Fluorodeoxyglucose (FDG)	Glucose metabolism	■ Standardised uptake value (SUV) ■ Tumor to background uptake ratio ■ Metabolic rate of glucose	Up-regulation of GLUT-1 transporters and hexokinase II activity Some normal tissue have background activity – e.g., brain, liver
^{15}O-Water	Perfusion	■ Perfusion (ml/(g*min)) ■ Standardised uptake value ■ Tumor to background uptake ratio	Angiogenesis, vascularity, blood flow
^{18}Fluorothymidine (FLT)	Cellular proliferation	■ Standardised uptake value ■ Tumor to background uptake ratio	Activity of cytosolic thymidine kinase Incorporation into newly synthesized DNA Does not cross blood brain barrier
^{124}I Annexin-V	Apoptosis	■ Standardised uptake value ■ Tumor to background uptake ratio	Exposure of phospatidylserine in the cell membrane during programmed cell death
^{99}TCm Methoxyisobutyl-isonitrile (MIBI)	pGlycoprotein mediated multi-drug resistance	■ Tumor to background uptake ratio	Ejection of cytotoxic drugs from tumor cells
^{18}Fluoromisonidazole (MISO)	Hypoxia	■ Tumor to blood ratio	Tissue oxygenation Nitroreductase activity
Copper-diacetyl-bis (N4-methylthiosemicarbazone) (Cu-ATSM)	Hypoxia	■ Tumor to muscle ratio	Tissue oxygenation
^{11}C-choline and ^{18}F-choline	Cellular proliferation	■ Standardised uptake value ■ Tumor to background uptake ratio	Cell membrane synthesis and breakdown
^{18}F-FET and ^{11}C-methionine	Amino acid metabolism	■ Standardised uptake value	Indicates proliferative activity Useful for brain tumor recurrence

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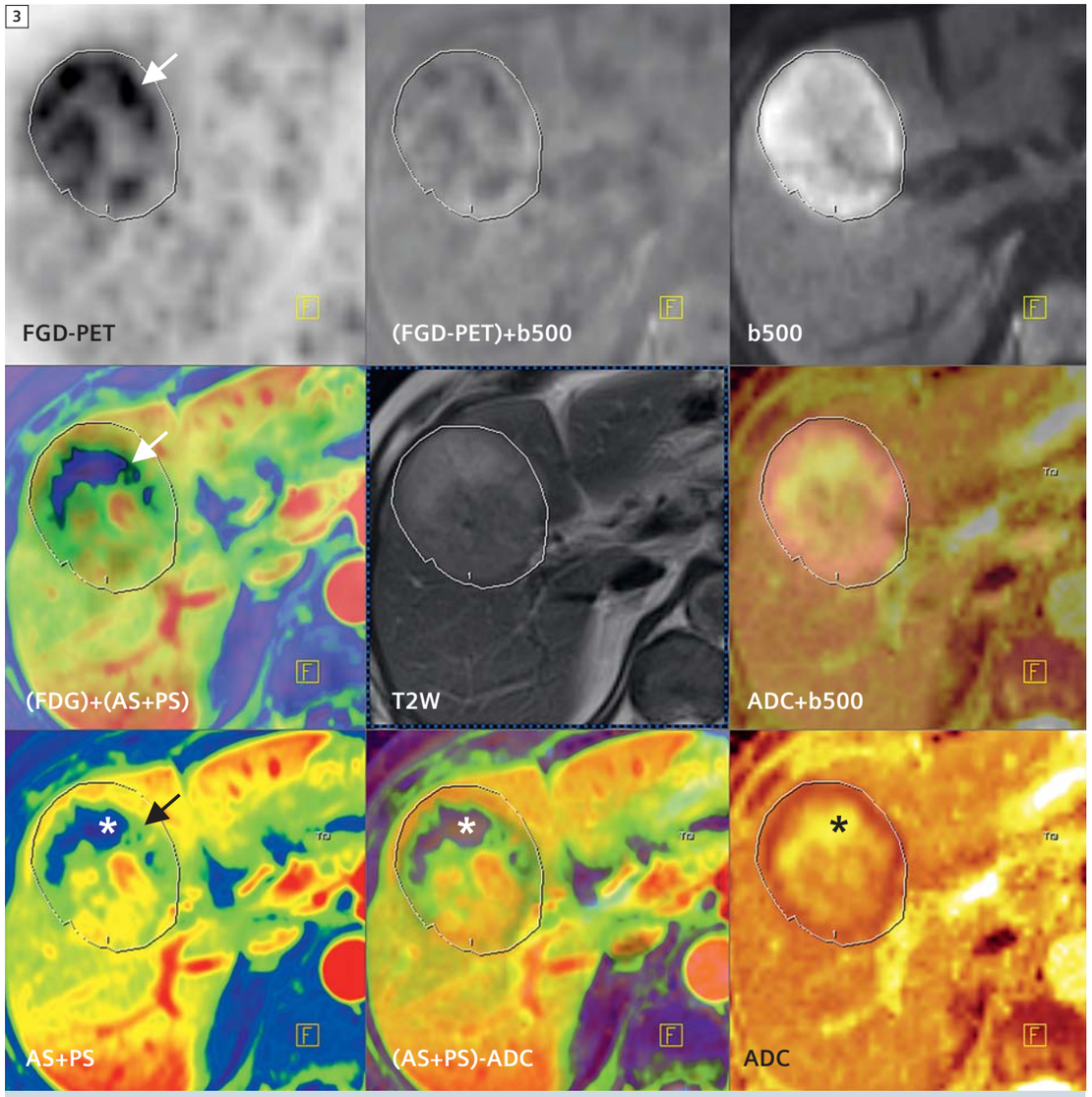
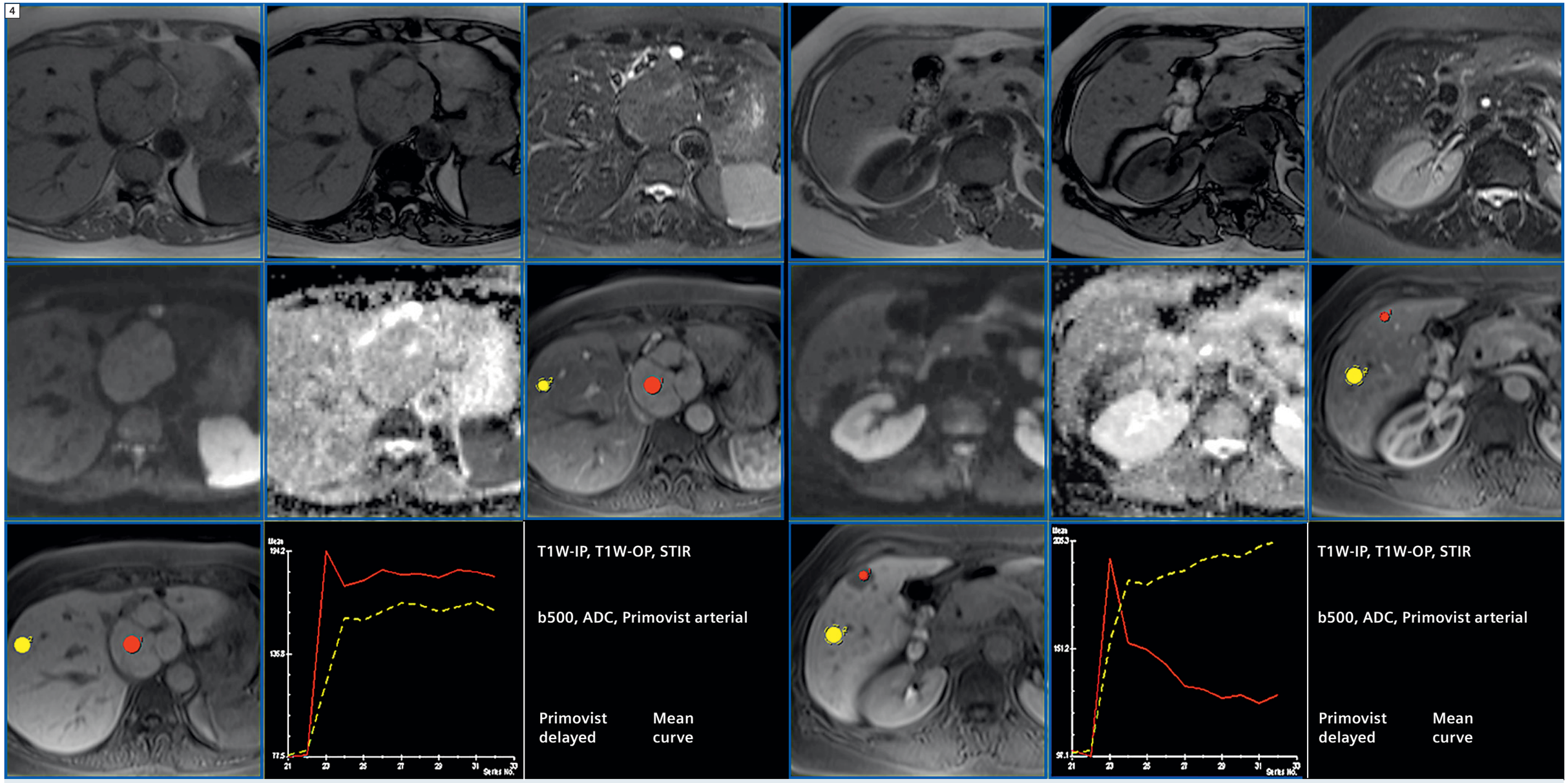


3 Fusion imaging of MRI and FDG-PET.
56-year-old male with metastatic colorectal cancer to the liver. Morphological T2-weighted, DW-MRI (b500 and ADC), DCE-MRI (arterial slope (AS) and portal slope (PS) added to yield total flow) and ^{18}FDG-PET scans were combined using fusion software. Region of interest around the tumor outline on the b500 images was copied onto all images to aid cross correlations. The area of non-enhancement (*) on the (AS+PS) image has the highest ADC values indicating necrosis. Around the area of necrosis, perfusion is decreased (green color) compared to adjacent normal liver (yellows and reds). Note that FDG uptake is greatest at the edge of necrosis in the low vascularity area (arrows) possibility related to upregulated glucose transporters (Glut-1) secondary to hypoxic stress. Higher cellular density (low ADC values) coincides with well vascular tissues where FDG uptake is relative similar to that of the liver.



Fibro Nodular Hyperplasia (FNH)

Liver adenoma

4 Multiparametric MRI for liver lesion characterization. Two benign liver lesions (Fibronodular hyperplasia (FNH) and adenoma) evaluated by multifunctional MRI. Each lesion is depicted using T1w sequences (in-phase and opposed-phase), STIR sequences, DW-MRI (b500 and ADC) and DCE-MRI using a liver specific contrast agent Gadoxetic acid (Eovist in the USA and Primovist outside the USA). The different curve shapes on DCE-MRI reflect the relationship between histological structure (atretic canaliculi in FNH and no biliary canaliculi in adenomas) and functionality of contrast media transporters present on the portal and biliary sides of hepatocytes. Such structural-functional relationships can be used to more confidentially characterize liver lesions.

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Roles of multiparametric imaging

A review of the current literature shows that the multiparametric approach is used in a number of clinical areas:

(1) For the improved depiction of biological features

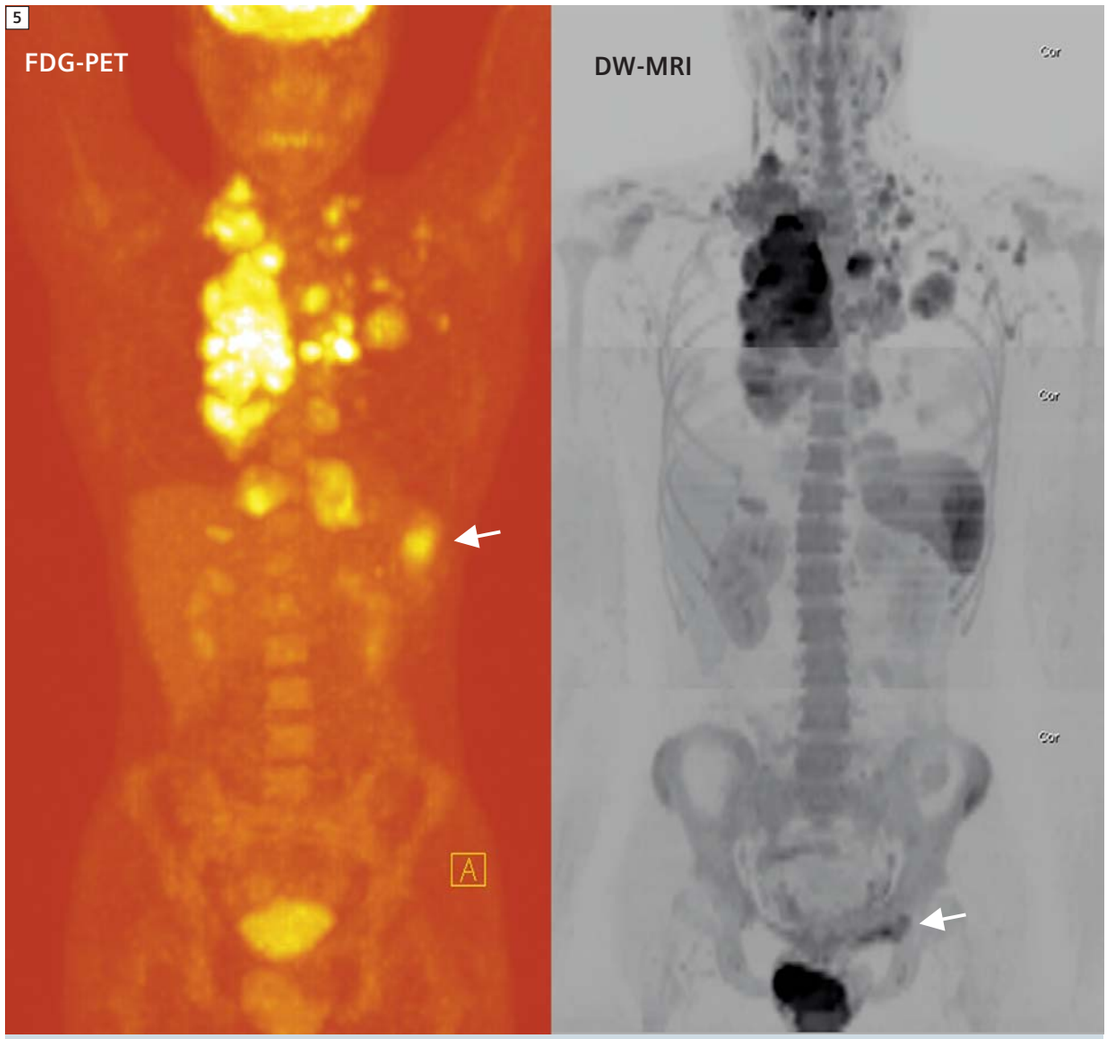
Multifunctional evaluations make it possible to correlate observations between imaging biomarkers at the tumor or voxel levels. Such cross correlations can be used to:

- refine the interpretation of imaging observations made by one technique using corresponding data from another. An example is the improved depiction of tissue oxygenation using BOLD-MRI by using blood volume distribution from DSC-MRI (Padhani, Krohn et al. 2007).
- To validate an emerging biomarker against an accepted standard (by ascertaining the strength of relationships between them and by exploring the circumstances under which the strength of relationships may be changed). For example, transfer constant from DCE-MRI can serve as a biomarker of tumor blood flow before therapy (because of a high first pass extraction of low molecular weight constant agents in tumors). However, in the brain (because of an intact blood brain barrier) or when tumors are successfully treated, transfer constant becomes a biomarker of vascular permeability.
- To clarify the spatial relationships between depicted biological functions at the voxel level, so as to gain insights into the consequences of tumor metabolic reprogramming (Figure 3). For example, correlating tissue oxygenation and perfusion or perfusion and glucose metabolism has been shown to be useful for tissue characterization and for predicting therapy response as discussed below.

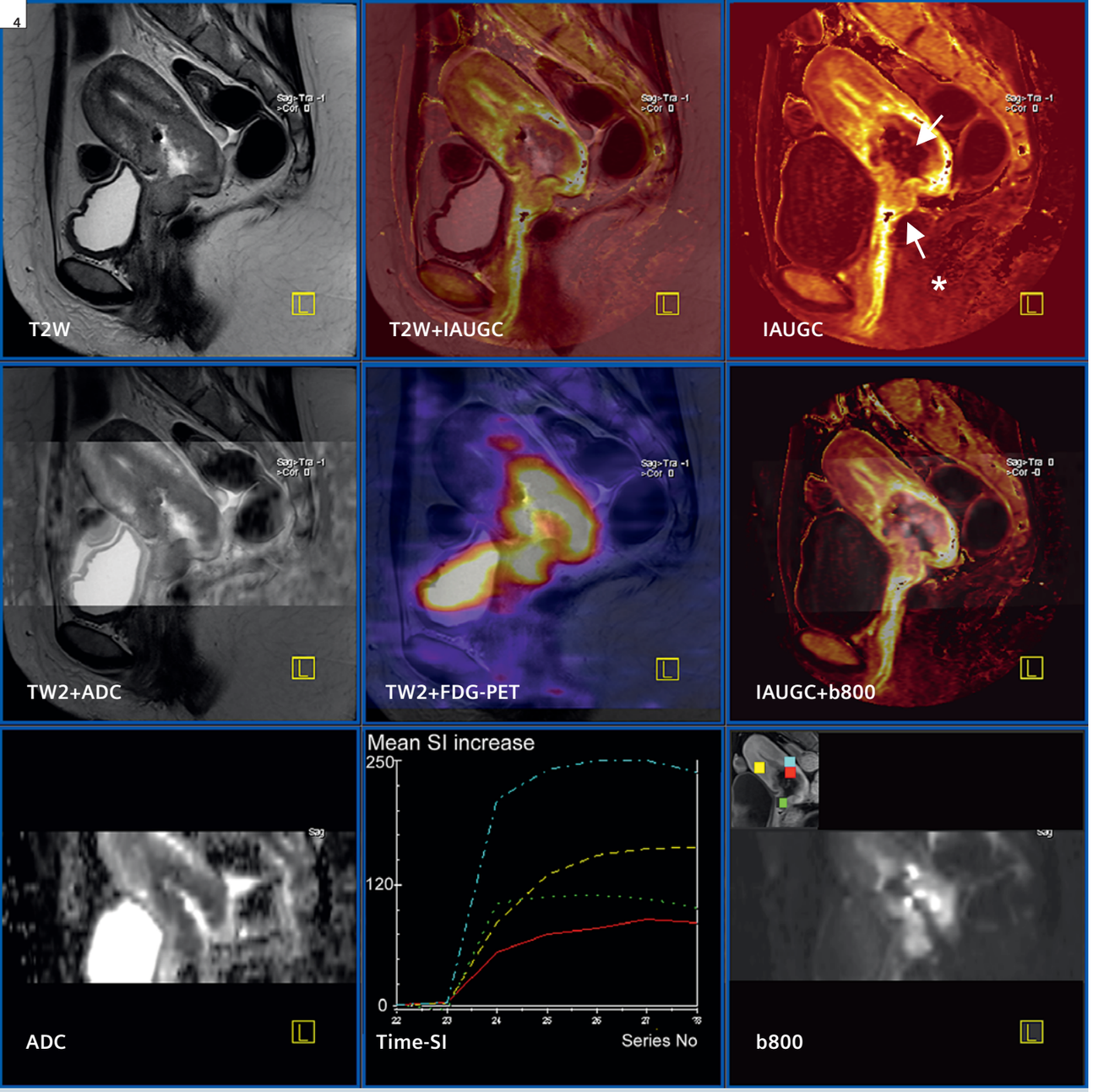
(2) For clinical characterisation of known disease

Functional-molecular imaging is often used to clarify the nature of abnormalities seen on morphological tests such as a CT or ultrasound scan. Multifunctional evaluations are a natural extension of this approach which has found roles in the characterization of lesions at a variety of anatomical sites including the brain, salivary glands, liver and prostate gland. So if an indeterminate liver lesion is found using anatomic CT/US imaging, then a multifunctional MRI scan maybe performed (including chemical shift imaging, diffusion MRI and dynamic contrast enhancement with a non-specific or liver specific contrast agent) (Figure 4). An unhelpful MRI scan may result in the use of a further imaging test such as an ^{18}FDG-PET for further clarification. When multifunctional assessments are used for disease detection and characterisation, it maybe found that individual modalities are discordant at the regional or tumor level. Discordance can occur because of tumor biology (see below) or for technical reasons including the fact that individually techniques have areas of strength and weakness, which can be overcome by combining imaging modalities together. An example is the improved staging of lymphoma by the combined use of ^{18}FDG-PET and diffusion-weighted MRI (DW-MRI). ^{18}FDG-PET is not sensitive enough for the detection of bone marrow infiltration which can be partially overcome by using DW-MRI. On the other hand DW-MRI is not sensitive enough to detect splenic disease which can be detected by ^{18}FDG-PET (Figure 5).

Discordant results can also be biologically meaningful often provoking new lines of investigations into tumor structural-functional relationships. For example, a number of studies have evaluated the relationship between glucose metabolism (^{18}FDG-PET) and tissue perfusion (which can be done with ^{15}O-water-PET, perfusion-CT and dynamic susceptibility contrast MRI (DSC-MRI). The recently introduced capability to perform perfusion-CT/^{18}FDG-PET has broadened the availability of this multiparametric approach. Although tightly coupled in most normal tissues, many studies have shown that the relationships between blood flow and glucose metabolism is not well matched in all tumors. Flow-metabolism mismatches have been shown in many tumor types depending on spatial location within tumors, on tumor type and grade, size and stage (Miles and Williams 2008). Miles and Williams suggested that low vascularity with high glucose uptake represents appropriate metabolic tumor adaptation to hypoxic stress whereas low vascularity with low glucose uptake represents a failure of tumor adaptation (Figures 6). Importantly the adaptive response (i.e., high glucose metabolism relative to blood flow) has been shown to be associated with poorer patient outcomes in breast and pancreatic cancers (Mankoff, Dunnwald et al. 2009). In the future, we can expect multifunctional-molecular imaging with PET-MRI systems to enable similar correlations between other biological processes to be undertaken, so as to gain greater insights into structural-functional relationships in health and disease and how these are altered in response to therapy.



5 Improved lymphoma staging with whole-body ^{18}FDG-PET and DW-MRI. 23-year-old male with Hodgkin's lymphoma. Nodal distribution of disease between whole-body ^{18}FDG-PET and DW-MRI is very similar. The ^{18}FDG-PET scan shows a splenic deposit (arrow on the PET scan) which is not visible on the DW-MRI (where only normal increased signal intensity is seen). On the other hand the bone marrow abnormality seen in the left superior pubic ramus on the DW-MRI (arrow) is not appreciated on the PET scan. Both lesions were unproven histologically because their presence does not affect the therapy to be given. There is some variation in the signal intensity of the top station of the DW-MRI compared to the middle and lower stations.



6 **Fusion imaging of morphology MRI with DW-MRI, DCE-MRI and ^{18}FDG-PET** 30-year-old female with non-metastatic poorly differentiated squamous carcinoma of the cervix. T2-weighted and DCE-MRI (initial area under gadolinium curve – IAUGC) was performed in the sagittal plane. DW-MRI (b800 s/mm^2 and ADC maps) and ^{18}FDG-PET scans were acquired in the axial plane and reconstructed into the sagittal plane. Top row images (left to right): T2-weighted (T2w), T2w image fused with initial area under gadolinium curve (IAUGC) and IAUGC maps. Middle row (left to right): fused T2w with ADC, T2w image fused with FDG-PET scan and IAUGC fused with b800 image. Bottom row (left to right) ADC map, time signal-intensity curves for regions of interest indicted in small insert on top of the b800 diffusion-weighted image. Note that the entire tumor depicted on T2w image is hypercellular (high signal intensity on b800 image and low on ADC map), hypermetabolic on the PET scan but the degree of vascularity is not uniformly distributed. The large hypovascular region (down arrow; red curve on the time-SI curves) has high glucose metabolism (adaptive response) which is likely to be more hypoxic than the anterior lip of the cervix (upward arrow with *) which is more vascular (green line). It is in adaptive areas (low flow with high glucose metabolism) where more aggressive tumor cell clones have been noted to emerge.

(3) Improved understanding of the biological effects of therapies

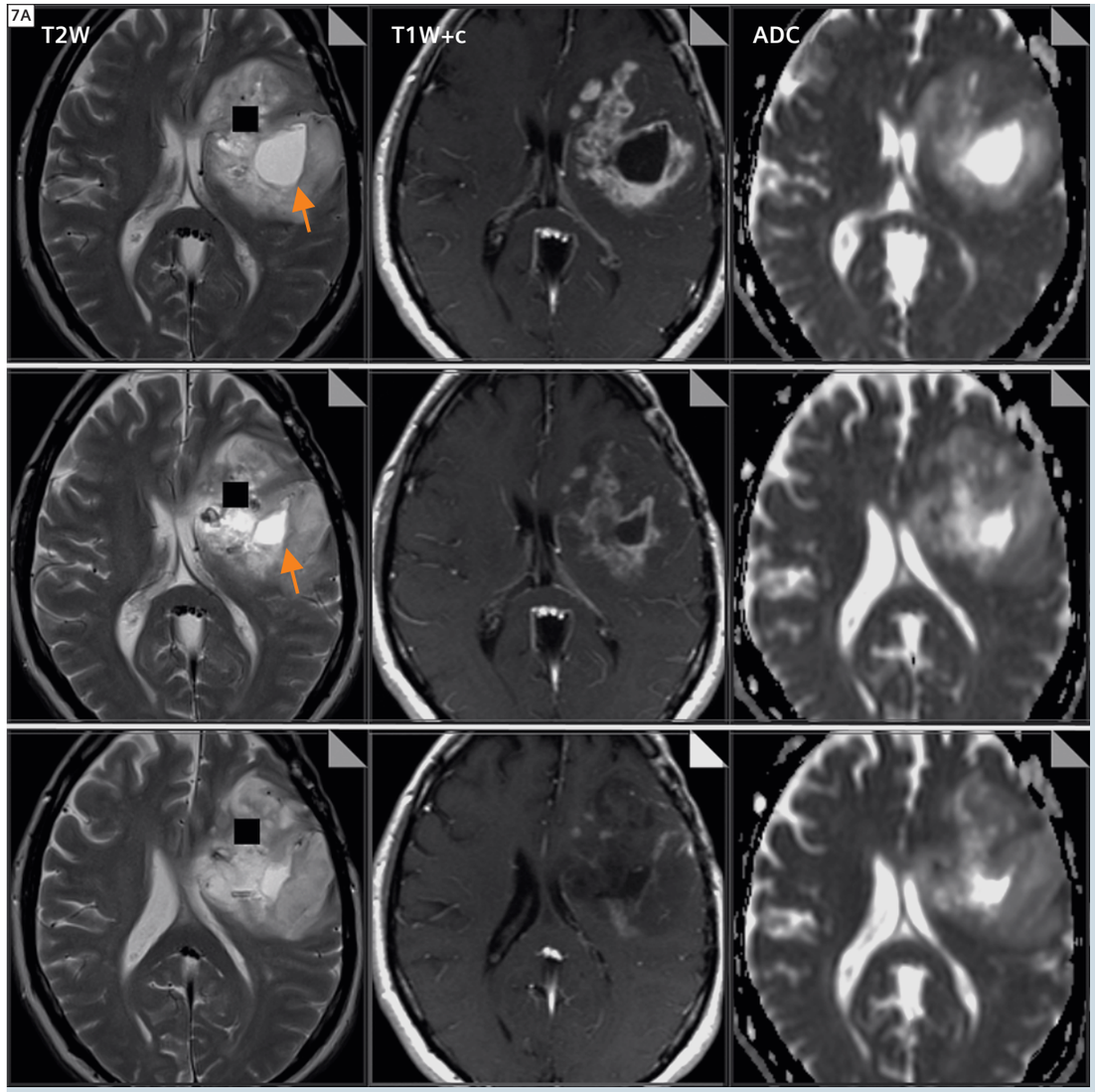
Monitoring changes during therapy with multifunctional imaging can provide invaluable information on the *in-vivo* mechanisms of action of therapeutics and of likely patients' outcomes. A number of studies have reported on the multiparametric approach for monitoring the effects of conventional therapies and for drugs with novel mechanisms of action. With respect to the latter, large numbers of new therapeutics are being developed as a result of the improved understanding of the molecular and genetic pathways controlling cellular function. Targeted molecular approaches typically seek to inhibit specific characteristics that are specific to cancers. As the pharmaceutical industry moves towards increasingly complex multi-targeted therapies, the anticipated effects on tumor tissues *de-novo* has become more difficult to predict. There is a growing recognition that biomarkers (including those derived from functional-molecular imaging) will play increasingly important roles in the drug development process (Figure 1). Imaging biomarkers can be used to confirm mechanisms of action of drugs *in-vivo* in early phase pre-clinical and clinical studies. Such pharmacodynamic (PD) data can then be potentially be harnessed for making "go-no-go" decisions at early stages of drug development; an important aim of which is to reduce the risk of failure of higher cost pivotal trials.

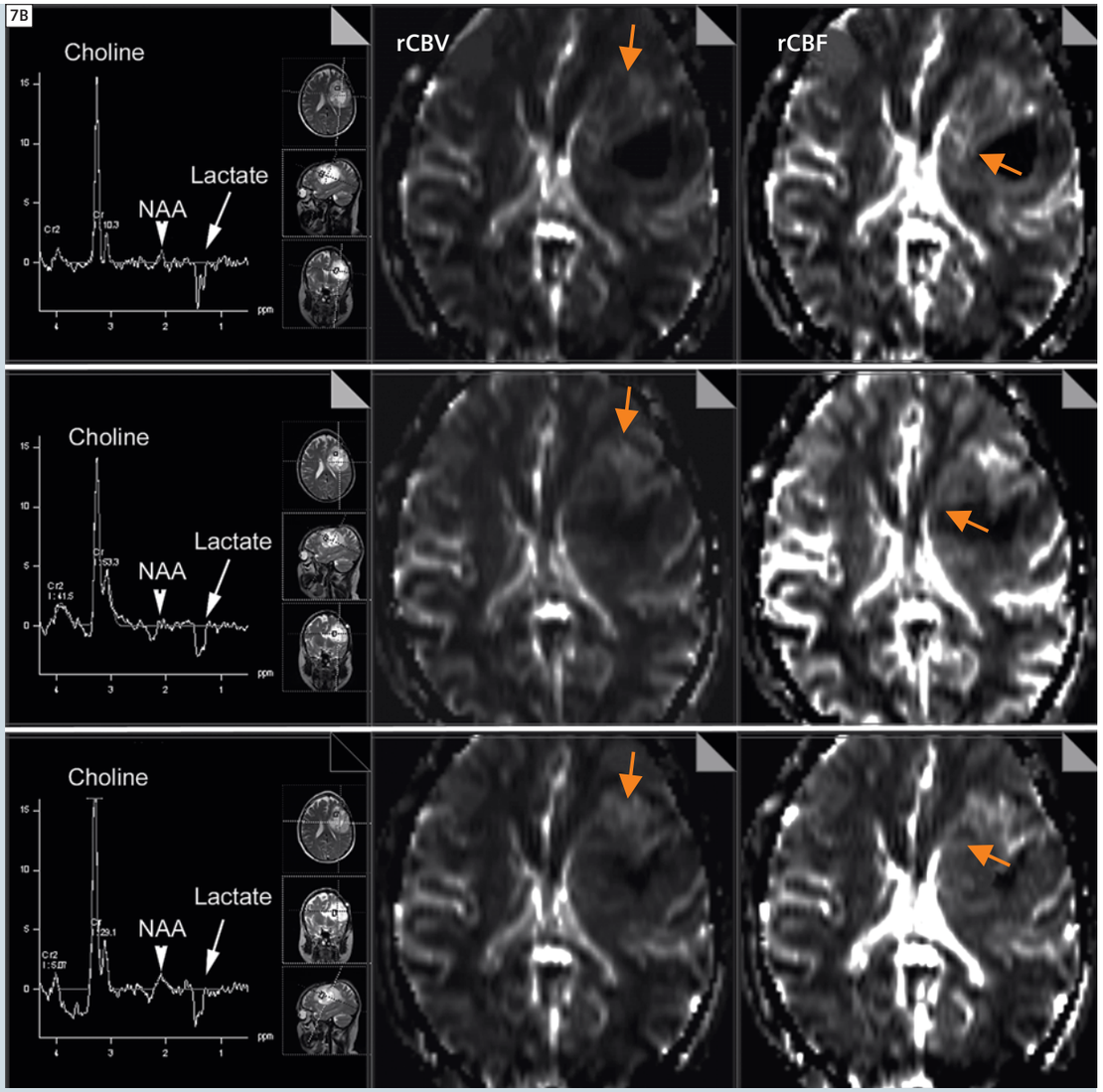
It is increasing being recognized that multiple tumor microenvironmental characteristics such as oxygenation levels, perfusion, extracellular pH, glucose metabolism and interstitial pressure as well as host-tumor interactions are important determinants of response to therapy, also determining the subsequent development of therapy resistance. For example, Batchelor et al. recently evaluated the antiangiogenic drug cediranib, given as monotherapy to patients with recurrent glioblastomas (Batchelor, Sorensen et al. 2007). Multiparametric MRI assessments showed rapid reductions in transfer constant, extracellular leakage space, and water diffusivity following treatment as the blood brain barrier became normalized. These effects were seen only in the enhancing volume of the tumor indicating that microenvironmental factors are determinants of therapy response. Interestingly, the enhancing tumor which had initially decreased in volume began to expand despite persistent decreases in microvessel permeability (pseudoresponse) suggesting that therapy resistance had developed (Figure 7). The mechanisms for the development of therapy resistance to antiangiogenics and other novel therapies are still being evaluated and will certainly include microenvironmental factors and host-tumor interactions. The ability to image the development of adverse characteristics leading to therapy resistance might enable us to develop strategies to circumvent such tumor adaptations, for the benefit of patients.

(4) Radiation therapy planning

Advances in imaging hardware related to radiation delivery have led to improvements in the physical conformality of radiation planning, treatment and delivery to tumors and organ boundaries using conformal and intensity-modulated techniques. The additional ability to combine image-depicted biology with image-guided radiotherapy has opened the way for further refinements of target definition and dose delivery, such that it is now possible to shape-dose volume distributions not only to the geometry of targets but also to differences in the radiobiology across tumors. Imaging-depicted radiobiologically relevant characteristics include tumor grade, hypoxia, acidosis or cellular proliferation.

Multiparametric imaging can potentially bring real benefits for radiation therapy planning in patients with brain gliomas where tumor delineation and gauging the aggressiveness of cancers by conventional contrast enhanced MRI/CT is severely limited (Dhermain, Hau et al. 2010). Uncoupling between tumor cell distribution and tumor grade makes it difficult to define effective, yet safe, margins for radiotherapy using conventional imaging. Uniform margins will either cover too much uninvolved brain (potentially exposing eloquent brain regions to unnecessary high radiation doses) or leave areas of tumor infiltration outside the treatment volume. This conundrum can potentially be overcome by multiparametric imaging; for example by combining ^{11}C-methonine PET with morphological MRI for tumor delineation and tumor grade mapping with perfusion MRI or ^{1}H-MR Spectroscopy (MRSI). This means that PET-MRI-planning CT scans ultimately need to be mapped onto the same frame reference for the purpose of brain radiation planning. In this regard, a combined MRI-PET scanner has obvious advantages minimizing the number of steps that use image co-registration software for data fusion and to correct geometrical distortions. Proof of concept studies, mostly retrospective, have shown that such multiparametric approaches can influence the placement of radiation treatment fields for glioma patients with the potential to improve treatment outcome (Dhermain, Hau et al. 2010), because the additional functional information is expected to increase the accuracy of target and normal tissue delineations. Validation of the efficacy of this new imaging-treatment approach will be needed, if this new paradigm is to become standard of clinical care.





7 Multiparametric MR imaging of anti-VEGF antibody therapy. 40-year-old man with a high grade glioma before and during anti-VEGF antibody therapy. Rows: serial images obtained before, after 14 days and after 12 weeks of bevacizumab therapy. Figure 7A shows serial changes in morphology (T2w), contrast enhancement (T1w+c) and diffusion MRI (ADC). Figure 7B shows serial changes in MR spectroscopy (TE = 135 ms) and relative blood volume (rBV) and flow (rBF).
Row 1: pre-bevacizumab. The T2w image shows a large tumor with necrotic region (arrow). The T1 post-contrast image shows areas within the tumor where the blood-brain-barrier has broken down and other areas where no enhancement is seen. The ADC map shows areas of low ADC (similar to brain) and very high ADC regions indicating necrosis. The MR spectrum taken from the region of the black box region on the T2w image, demonstrates a large choline (Cho) peak which correlates with hypercellularity, a reduced N-acetylaspartate (NAA) peak showing that neurons have been destroyed or displaced, and an inverted lactate acid (Lac) peak indicating anaerobic glycolysis.

Row 2: 14 days post-bevacizumab. Some reduction in the size of the mass is seen particularly of the necrotic component on the T2w image. A marked reduction in contrast enhancement indicates that capillary permeability has been reduced but the MRSI has remained unchanged indicating that there has been no cell death. Note that there has been some reduction in relative cerebral blood flow (upward pointing arrow) in a small region of the tumor.
Row 3: 12 weeks post-bevacizumab. The tumor has increased in size and thickness by growing into the area of necrosis. Again there is a reduction in enhancement indicating an on-going anti-permeability effect of bevacizumab. MRSI has not changed indicating the absence of tumor cell kill confirmed by the lack of change in the tumor ADC map. Increasing relative blood volume and flow (down pointing arrow) is consistent tumor progression also.

Challenges for implementation

Multifunctional imaging observations reinforce the underlying message of this review, that it is only by combining biomarker data from a number of imaging techniques that one may begin to truly understand how tumors interact with the host and how therapies affect tumor cells and tissue microenvironments. Such observations can also provide unique insights into the mechanism of drug action *in-vivo* and useful pharmacodynamic information. However, if functional-molecular imaging is to take up its unique position of enhancing decision-making at critical milestones in drug development, or in personalized medicine where therapy is adapted according to tumor-host phenotype or in novel radiation therapy planning, then procedural rigor and validation will be needed to establish biomarker-combinations for such roles.

It is possible to acquire spatially-matched multiparametric imaging data in potentially every patient at a given time point. Currently, integration of multidimensional imaging datasets represents a major challenge. If multiparametric data is acquired several times during a treatment, then there is an added level of complexity brought on by changing morphological features and patient repositioning. Sophisticated, user-friendly software workspaces need to be developed urgently, in order to be able to integrate/cross correlate data analysis procedures so as to follow changes in response to therapy. Computer platforms need to incorporate bioinformatics approaches, so that imaging biomarkers can be correlated with findings from immunohistochemistry, gene expression profiles, and tissue and clinical biomarker data. Ultimately, multispectral imaging analyses should be able to generate probability biomaps of important biological characteristics or to infer underlying molecular gene expression patterns. Composite biomaps incorporating functional imaging would be invaluable in lesion characterisation, therapy planning and for assessing the effects of therapies.

Conclusions

When considering the potential opportunities for multiparametric imaging to influence patients' management, it should be remembered that the perceived advantages of such approaches are currently without a sound evidence base regarding selection of patients who would benefit from these more complex approaches, and whether improved patient outcomes will ultimately be seen. Furthermore, functional-molecular imaging techniques are at different stages of development with incomplete validation or acceptance of standards for data acquisition and analysis. Frameworks for the validation of functional-molecular imaging to support clinical decision making are only now beginning to emerge. Additionally, there are practical challenges for incorporating both anatomical-functional-molecular into therapy paradigms including image-guided radiotherapy systems, which will need to be overcome. However, we can state with some confidence that there are extraordinary opportunities for multiparametric imaging approaches to evolve into qualified biomarkers that are useful clinically, for pharmaceutical drug development, radiation therapy planning and for predicting therapeutic efficacy. Multidisciplinary efforts will be required to bring this vision into fruition.

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